REPORT TITLE

Endosulfan Task Force Response to the Health Effects Division
Response to Comments generated in Phase 4 for the Endosulfan RED
(DP Barcode D279252; Memo from Diana Locke, Ph.D., dated January 18, 2002)

DATA REQUIREMENT

Not Applicable

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STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS

No Claim of Confidentiality is made for any information contained in this report on the basis of its falling within the scope of FIFRA 10 (d)(1)(A), (B), or (C).

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STATEMENT OF GOOD LABORATORY PRACTICE

No Good Laboratory Practice Statement is required for the information presented in this volume according to 40CFR Part 160.

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Date: January 28, 2002

ENDOSULFAN TASK FORCE RESPONSE TO THE HED's RESPONSE TO COMMENTS GENERATED IN PHASE 4 FOR THE ENDOSULFAN RED

RE: Response to Comments on EPA's Human Health Risk Assessment of Endosulfan 01/31/01, PC Code: 079401, Case # 819236, DP Barcode D279252; Memo from Diana Locke, Ph.D., dated January 18, 2002

The Endosulfan Task Force (ETF) appreciates the effort HED has put into reviewing the Phase 3 comments from the ETF as well as other stakeholders, and we welcome the opportunity to comment on it. Our comments mainly pertain to Section V, *"Toxicology – Endocrine Disruption"* and Section VII *"Incident Data"* of the subject document.

EPA RESPONSE TO COMMENTS:

Page 4-6, Section V. Toxicology: *Endocrine Disruption*

In the initial draft of the HED Toxicology Chapter for the Endosulfan RED, the Agency provided a weight-of-evidence document regarding the potential for endosulfan to be an endocrine disruptor (Liem D. (11-24-98), Appendix A of HED DOC Number: 014049, dated November 12, 1999). The ETF has submitted two responses concerning endocrine disruption and endosulfan (MRID# 44939102, dated October 4, 1999; and MRID# 45300203, dated January 5, 2001). The Agency reviewed the first of these documents (E. Mendez, December 11, 2000), which has provided the basis for their response to comments and are discussed below. However, the ETF request that the Agency also reviews the second ETF response that included a detailed summary and evaluation of many of the newest public literature citations regarding hormonal interactions and *in vivo* reproductive organ effects, which the Agency refers to in their response.

EPA comments: EPA's suggestion that Endosulfan is an Endocrine Disruptor

In response to the first ETF report (MRID# 44939102) regarding endocrine disruption and endosulfan, the Agency provided the following comment:

> *The Agency identifies an environmental endocrine disruptor as an exogenous agent that interferes with the synthesis, secretion, transport, binding action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior.*[1] *Based on these criteria, the Agency disagrees with the conclusion by the registrant that endosulfan does not meet the definition of an endocrine disruptor.*

[1] Crisp, T.M. *et al.* *Environmental Endocrine Disruption: An Effects Assessment and Analysis.* Environmental Health Perspectives 106 pp. 11-56.

Binding to the estrogen receptor is only one potential mode of action for endocrine disruptors, namely direct interaction with a receptor in the target cells. Substances that act as endocrine disruptors may perturb the endocrine system in a variety of ways including but not limited to interfering with the synthesis, secretion, or transport of hormones in the organism. Some examples of endocrine disruption that do not involve receptor binding are: 1) depression of the steroidogenic enzymes and cytochrome P450 dependent monooxygenases, which suggests that conversion of cholesterol to testosterone may be affected by endosulfan; 2) decreases in luteinizing hormone (LH) activity that may result in decreases in the activity of Steroidogenic Acute Regulatory Protein responsible for translocation of cholesterol from the cytosol to the inner mitochondria [transport and synthesis affected]; and 3) effects on the sex hormone binding globulin (SHBG) as indicated by decreases in plasma and testicular testosterone in conjunction with serum testosterone [effect on hormone transport].[2]

Consequently, the absence of high binding affinity to the estrogen receptor should not be interpreted as lack of endocrine disruption potential. The Agency notes that other organochlorines (i.e. DDT, DDE, dieldrin, and methoxychlor) have been demonstrated to interact with the endocrine system in spite of differing binding affinities to the estrogen receptor.

Finally, the registrant states that no effects were reported after administration of endosulfan on the endocrine, reproductive or sexually regulated systems at doses causing clear toxicity. However, it is noteworthy that testicular atrophy was reported during a Chronic Oral Toxicity Study in Rats (MRID# 00004256) submitted to the Agency. Additionally, increased pituitary and uterine weights were also observed during a Multi-Generation Reproduction Study (MRID# 00148264). Furthermore, an increase in the incidence of parathyroid hyperplasia was also reported during the Chronic Oral Toxicity study in Rats.

ETF response:

The definition of an endocrine disruptor provided by the Agency in this response differs in specificity from the currently accepted definitions provided by the EDSTAC and the OECD. However, even when using the Agency's stated definition, the weight-of-evidence provided by the full spectrum of public literature and guideline studies continues to support the ETF's conclusions that endosulfan is unlikely to be an endocrine disruptor in humans.

The examples of indirect endocrine action cited by EPA in this response were addressed in the ETF document submitted in January 2001 (MRID# 45300203). In the ETF document a summary of the available public literature in vivo and ex vivo androgenic assays was provided, giving the endpoints evaluated and the results. In most cases the administrated dose in these studies was within the systemically toxic range for endosulfan, based on guideline subchronic exposure studies. In the majority of these

[2] ATSDR Toxicity Profile for Endosulfan. September, 2000.

studies evaluation of potential liver and kidney toxicity was not conducted, thereby severely limiting the ability to assess the relevance of the stated findings. While the Agency has included indirect effects within the scope of defining endocrine disruption, if the effects noted are secondary to frank toxicity of key homeostatic organ systems, the relevance to human risk is highly questionable.

While the Agency has hypothesized potential mechanisms of action for endosulfan resulting in decreased testosterone levels via indirect actions on synthesis, secretion and transport, there is no clear evidence from the public literature or guideline toxicity data to support these suppositions. Endosulfan does cause liver enzyme induction, which is known to result in increased steroid metabolism and clearance (Wilson, 1997; Singh SK and Pandey RS, 1989a and 1990). In addition, new investigations using juvenile rat Leydig cells showed no effect of endosulfan on testosterone levels or conversion of 22(R)hydroxycholesterol to testosterone (Murono EP, 2001). Therefore, the decrease in testosterone levels, seen at doses known to cause liver and kidney toxicity (Dikshith et al. 1984; Singh and Pandey 1989b), is more likely a direct result of increased metabolism and excretion of steroid hormones, than a protracted effect on synthesis, secretion and transport.

The ETF agrees with the Agency that definitive determinations of endocrine disruption can not be derived solely from *in vitro* receptor binding assays. These assays are one part of a comprehensive weight-of-evidence evaluation that includes *in vitro*, *in vivo* and *ex vivo* data. Overall, endosulfan has shown weak binding affinity in several *in vitro* estrogen receptor-binding assays, but was negative in four different uterotrophic assays, was inconclusive in numerous androgenic assays, and was negative in both developmental and reproductive *in vivo* studies. In addition, the ETF has emphasized in the past that it is not appropriate to compare endosulfan to organochlorines. Endosulfan is metabolized more readily, does not bioaccumulate and does not interact synergistically with compounds such as dieldrin, DDT, DDE, DDD, toxaphene or chlordane in estrogenic assays.

Lastly, the Agency mentioned potential effects noted in a 1978 NCI chronic oral toxicity study in rats (MRID# 00004256), as well as uterine and pituitary weight changes seen in the two-generation rat reproductive toxicity study (MRID# 00148264). Again, these issues were discussed in detail in the EFT January 2001 response (MRID# 45300203). Briefly, the effects cited by the Agency from the 1978 National Cancer Institute (NCI) in rats study, which did not meet EPA's guideline acceptance criteria, included testicular atrophy and parathyroid hyperplasia. However, these results were due to frank systemic toxicity that was seen at both the low and high dose, mortality rates of 38% and 50% resulted in termination of dosing at 74 and 82 weeks, respectively. Male rats in both dose groups showed significant liver toxicity and chronic renal failure. The parathyroid hyperplasia was considered to be secondary to chronic renal failure. As stated previously, severe intoxication, which involves organs such as the liver and kidney results in significant disruption of physiological homeostasis and indirect effects on the major endocrine axes. In addition, there is no indication of these types of effects occurring in guideline accepted chronic studies in rats where the MTD was met, but not exceeded.

The purpose of the multi-generation reproductive toxicity study in rats is to measure possible disturbances of reproductive performance, development and maturation including development of sex organs (vaginal opening, cryptorchidism, etc.) at doses up to and including parental toxicity. Endosulfan, administered to both male and female rats, did not cause such interference through two successive generations (MRID# 00148264). There was an indication of weight effects on the pituitary gland of the F_0 pups of the first mating and uterus of the F_{1b} pups from the first mating. These effects are of limited significance since neither the pituitary or uterus was seen as a target organ in any other study, there was no supporting histopathological changes noted, nor were these effects consistent across generations. In addition, four separate uterotrophic assays were negative for uterine effects at doses up to 100 mg/kg bw/day, suggesting that the weight-of-evidence is negative for specific endocrine effects on the uterus. Lastly, the statistically significant increase in pituitary weights was due to a single female in the high dose group.

The ETF believes that the data for endosulfan is complete and reliable, including four uterotrophic assays, which is the same assay currently undergoing validation for use as a regulatory screen. The weight-of-evidence from *in vitro* and *in vivo* screening tests and *in vivo* toxicity tests clearly show that endosulfan is not an endocrine disruptor. The ETF believes that until EPA establishes their own set of criteria for determining endocrine-related effects and has the opportunity to fully evaluate the available data for endosulfan, allegations concerning its potential as an endocrine disruptor should be deleted from the RED**.**

Page 10, Section VII: Incident Data, 1st paragraph

In HED's first draft of the endosulfan risk assessment (01/31/01, p.43: 7.4. Incident Data), the Agency was referring to US specific incident databases (J. Blondell, 2000), such as Incident Data System (IDS), Poison Control Center, California Department of Pesticide Regulations, and National Pesticide Telecommunications Network (NPTN) with the overall conclusion that *the data from these sources often lacked specific information on the extent of exposure and the circumstances of exposure. Collectively, however, the incidence information indicates definite poisoning risks from* <u>*misuse*</u> *of products that contain endosulfan, or from not wearing personal protective equipment.* In the newly revised preliminary HED Phase 4 response, HED is ignoring these earlier statements and interpretations by referring to the following:

EPA comments: *A quick MEDLINE/PubMed search at the National Library of Medicine web site, revealed 560 entries for endosulfan. Many recent entries use new multiresidue analytical chemistry measurement methods. Some poisonings date back to 1970 in Germany. The literature entries reflect mostly international pesticide poisoning incident case reports referred to by PAN Asia and the Pacific/ PAN North America*

{Docket #34242} and Ohio based Rural Action Safe Pest Control Program {Docket #34242}, and some studies appear to be consistent with the thrust of their concerns.

ETF response: The MEDLINE/PubMed web site actually lists 563 entries for endosulfan. After closer evaluation of the entries, it must be noted that out of the 563 listed abstracts only 15 were actually reporting about endosulfan related human poisinings; only one confirmed case was reported from the USA, the others were from foreign countries, such as Australia (1), Belgium (1), China (1), India (4), Israel (2), Poland (2), Spain (2), and Netherlands (1). Most of these reports were not related to agricultural uses/exposure; they were related to industrial (2), non-accidental incidents and misuse (7), route of exposure not identified (4). In many cases no conclusions can be drawn implicating endosulfan as the cause of the reported health effects (multi-pesticide residue exposure), some of the reporting is anecdotal and based on allegations and not facts.

Therefore the ETF feels, that HED's statement that there are 560 entries under the Section "Incident Data" is false and misleading, especially in view of the actual number of incidents caused from the registered use of endosulfan in the USA (1 case).

It is also inappropriate to use anecdotal information from foreign countries regarding the US regulatory assessment without any knowledge of the use conditions and circumstances of the findings (cause /effect relationship). Use pattern and product awareness differ from country to country. The use directions and the handling of the product are certainly different in Poland, Spain, China and India from those in the USA. Again, often the specific circumstances that have led to the reported illnesses (misuse, accidents, etc.) were not stated or identified.

Based on endosulfan's long use history in the USA (>40 years) and the available illness report databases (California-EPA 1982-1999, NPTN 1984-1991), the use of endosulfan has not caused any concern if the label directions are followed. In California, where the product use is relatively heavy and the mandatory incident reporting is very accurate, the illness surveillance program indicates that a total of 32 cases (1982-1999) were reported. Not one person was hospitalized and only 2 incidents of the 32 could be definitely related to endosulfan. Most of the injuries were minor (skin irritation/rashes, eye injuries, headaches, dizziness, weakness). Most of the other reports (30) could not identify a clear cause relationship. Overall, endosulfan was ranked 61st (California-EPA 1982-1999) and nationwide 65th (NPTN 1984-1991) concerning the reported human incidents that are related to pesticides.

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